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NEWS 10 Jun 10 MEDLINE Reload

NEWS 11 Jun 10 PCTFULL has been reloaded

NEWS 12 Jul 02 FOREGE no longer contains STANDARDS file segment

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saved answer sets no longer valid

NEWS 14 Jul 29 Enhanced polymer searching in REGISTRY

NEWS 15 Jul 30 NETFIRST to be removed from STN

NEWS 16 Aug 08 CANCERLIT reload

NEWS 17 Aug 08 PHARMAMarketLetter(PHARMAML) - new on STN

NEWS 18 Aug 08 NTIS has been reloaded and enhanced

NEWS 19 Aug 09 JAPIO to be reloaded August 25, 2002

NEWS 20 Aug 19 Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN

NEWS 21 Aug 19 IFIPAT, IFICDB, and IFIUDB have been reloaded

NEWS 22 Aug 19 The MEDLINE file segment of TOXCENTER has been reloaded

NEWS 23 Aug 26 Sequence searching in REGISTRY enhanced

NEWS EXPRESS February 1 CURRENT WINDOWS VERSION IS V6.0d,

CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP),

AND CURRENT DISCOVER FILE IS DATED 05

FEBRUARY 2002

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FILE 'HOME' ENTERED AT 09:53:39 ON 02 SEP 2002

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FILE 'CANCERLIT' ENTERED AT 09:54:18 ON 02 SEP 2002

=> S CD95 OR FAS OR APO-1  
L1 37622 CD95 OR FAS OR APO-1

=> S INCREAS? OR INDUC?  
3 FILES SEARCHED...  
L2 10247137 INCREAS? OR INDUC?

=> S L1(S)L2  
L3 22697 L1(S) L2

=> S EXPRESS?  
L4 2705546 EXPRESS?

=> S L3(S)L4  
L5 13033 L3(S) L4

=> S P53  
L6 104368 P53

=> S L5(S)L6  
L7 953 L5(S) L6

=> S CHEMOTHERAP?  
L8 439321 CHEMOTHERAP?

=> S L7 AND L8  
L9 112 L7 AND L8

=> DUP REM L9  
PROCESSING COMPLETED FOR L9  
L10 46 DUP REM L9 (66 DUPLICATES REMOVED)

=> S L10 NOT PY>1999  
L11 25 L10 NOT PY>1999

=> D TI SO 1-25

L11 ANSWER 1 OF 25 MEDLINE  
TI p53-mediated up-regulation of CD95 is not involved in genotoxic drug-induced apoptosis of human breast tumor cells.  
SO CELL DEATH AND DIFFERENTIATION, (1999 Mar) 6 (3) 271-80.  
Journal code: 9437445. ISSN: 1350-9047.

L11 ANSWER 2 OF 25 MEDLINE  
TI Boswellic acids and malignant glioma: induction of apoptosis but no modulation of drug sensitivity.  
SO BRITISH JOURNAL OF CANCER, (1999 May) 80 (5-6) 756-65.  
Journal code: 0370635. ISSN: 0007-0920.

L11 ANSWER 3 OF 25 MEDLINE

TI Sensitization of AIDS-Kaposi's sarcoma cells to Apo-2 ligand-induced apoptosis by actinomycin D.

SO JOURNAL OF IMMUNOLOGY, (1999 May 1) 162 (9) 5616-23.  
Journal code: 2985117R. ISSN: 0022-1767.

L11 ANSWER 4 OF 25 MEDLINE

TI Distinct p53-independent apoptotic cell death signalling pathways in testicular germ cell tumour cell lines.

SO INTERNATIONAL JOURNAL OF CANCER, (1999 May 17) 81 (4) 620-8.

Journal code: 0042124. ISSN: 0020-7136.

L11 ANSWER 5 OF 25 MEDLINE

TI The CD95/CD95 ligand system is not the major effector in anticancer

drug-mediated apoptosis.

SO CELL DEATH AND DIFFERENTIATION, (1998 Sep) 5 (9) 735-42.

Journal code: 9437445. ISSN: 1350-9047.

L11 ANSWER 6 OF 25 MEDLINE

TI p53 activates the CD95 (APO-1/Fas) gene in response to DNA damage by

anticancer drugs.

SO JOURNAL OF EXPERIMENTAL MEDICINE, (1998 Dec 7) 188 (11) 2033-45.

Journal code: 2985109R. ISSN: 0022-1007.

L11 ANSWER 7 OF 25 MEDLINE

TI Dexamethasone-mediated protection from drug cytotoxicity: association with

p21WAF1/CIP1 protein accumulation?

SO ONCOGENE, (1998 Sep 24) 17 (12) 1567-75.

Journal code: 8711562. ISSN: 0950-9232.

L11 ANSWER 8 OF 25 MEDLINE

TI Molecular determinants of apoptosis induced by cytotoxic drugs.

SO KLINISCHE PADIATRIE, (1998 Jul-Aug) 210 (4) 148-52.

Journal code: 0326144. ISSN: 0300-8630.

L11 ANSWER 9 OF 25 MEDLINE

TI Potentiation of CD95L-induced apoptosis of human malignant glioma cells by

topotecan involves inhibition of RNA synthesis but not changes in CD95 or

CD95L protein expression.

SO JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1998 Sep) 286 (3) 1374-82.

Journal code: 0376362. ISSN: 0022-3565.

L11 ANSWER 10 OF 25 MEDLINE

TI CD95-mediated apoptosis: no variation in cellular sensitivity during cell

cycle progression.

SO FEBS LETTERS, (1998 Aug 7) 432 (3) 155-7.

Journal code: 0155157. ISSN: 0014-5793.

L11 ANSWER 11 OF 25 MEDLINE

TI Retinoic acids induce growth inhibition and apoptosis in adult T-cell leukemia (ATL) cell lines.

SO LEUKEMIA RESEARCH, (1998 Jul) 22 (7) 611-8.

Journal code: 7706787. ISSN: 0145-2126.

L11 ANSWER 12 OF 25 MEDLINE

TI Transcription abnormalities potentiate apoptosis of normal human fibroblasts.

SO MOLECULAR MEDICINE, (1997 Dec) 3 (12) 852-63.

Journal code: 9501023. ISSN: 1076-1551.

L11 ANSWER 13 OF 25 MEDLINE

TI Hypericin-induced apoptosis of human malignant glioma cells is light-dependent, independent of bcl-2 expression, and does not

require wild-type p53.

SO NEUROLOGICAL RESEARCH, (1997 Oct) 19 (5) 459-70.  
Journal code: 7905298. ISSN: 0161-6412.

L11 ANSWER 14 OF 25 MEDLINE

TI Immunotherapy of malignant glioma: synergistic activity of CD95

ligand and chemotherapeutics.

SO CANCER IMMUNOLOGY, IMMUNOTHERAPY, (1997 Mar) 44 (1) 55-63.

Journal code: 8605732. ISSN: 0340-7004.

L11 ANSWER 15 OF 25 MEDLINE

TI Drug-induced apoptosis in hepatoma cells is mediated by the CD95 (APO-1/Fas) receptor/ligand system and involves activation of wild-type

p53.

SO JOURNAL OF CLINICAL INVESTIGATION, (1997 Feb 1) 99 (3) 403-13.

Journal code: 7802877. ISSN: 0021-9738.

L11 ANSWER 16 OF 25 MEDLINE

TI Apoptosis. Its significance in cancer and cancer therapy.

SO CANCER, (1994 Apr 15) 73 (8) 2013-26. Ref: 179

Journal code: 0374236. ISSN: 0008-543X.

L11 ANSWER 17 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

TI New insights into the kinetic resistance to anticancer agents.

SO Cytotechnology, (1998) Vol. 27, No. 1-3, pp. 225-235.  
ISSN: 0920-9069.

L11 ANSWER 18 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

TI Potentiation of CD95L-induced apoptosis of human malignant glioma cells by

topotecan involves inhibition of RNA synthesis but not changes in

CD95 or

CD95L protein expression.

SO Journal of Pharmacology and Experimental Therapeutics, (Sept., 1998) Vol.

386, No. 3, pp. 1374-1382.

ISSN: 0022-3565.

L11 ANSWER 19 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

TI p53 accumulation promotes dephosphorylation and proteolytic cleavage of

retinoblastoma protein in human malignant glioma cells.

SO Cellular Physiology and Biochemistry, (1997) Vol. 7, No. 6, pp. 304-311.

ISSN: 1015-8987.

L11 ANSWER 20 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

TI Genetic regulation and therapeutic modulation of apoptosis in human

malignant glioma.

SO Cellular Physiology and Biochemistry, (1996) Vol. 6, No. 6, pp. 376-380.

ISSN: 1015-8987.

L11 ANSWER 21 OF 25 CANCERLIT

TI 9-AMINOCAMPTOTHECIN INDUCES APOPTOSIS IN VITRO AND PROLONGS SURVIVAL OF

MICE WITH HUMAN RENAL CELL CARCINOMA

XENOGRAFTS (Meeting abstract).

SO Proc Annu Meet Am Soc Clin Oncol, (1998) 17 A1284.

L11 ANSWER 22 OF 25 CANCERLIT

TI Immunologic cytotoxicity overcomes p53-mediated resistance to apoptosis

(Meeting abstract).

SO Proc Annu Meet Am Assoc Cancer Res, (1997) 38 A3258.  
ISSN: 0197-016X.

L11 ANSWER 23 OF 25 CANCERLIT  
TI Expression of apoptotic genes in Pgp- and MRP-overexpressing tumor cells  
(Meeting abstract).  
SO Proc Annu Meet Am Assoc Cancer Res, (1997) 38 A1924.  
ISSN: 0197-016X.

L11 ANSWER 24 OF 25 CANCERLIT  
TI Bcl-2 and chemoresistance in cancer (Meeting abstract).  
SO Proc Annu Meet Am Assoc Cancer Res, (1995) 36 711.  
ISSN: 0197-016X.

L11 ANSWER 25 OF 25 CANCERLIT  
TI The bcl-2 gene family: expression and function (Meeting abstract).  
SO Non-serial, (1994) 10th International Symposium on Cellular Endocrinology:  
Molecular and Cell Biology of Apoptosis in Development, Disease and  
Cancer, September 29-October 2, 1994, Lake Placid, NY, p. 43,  
1994.

=> DIBIB AB 17,16,15,14,8,6,5,1

L11 ANSWER 17 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
ACCESSION NUMBER: 1999:104527 BIOSIS  
DOCUMENT NUMBER: PREV199900104527  
TITLE: New insights into the kinetic resistance to anticancer agents.  
AUTHOR(S): Chauffert, Bruno (1); Dimanche-Boitrel, Marie-Therese;  
Garrido, Carmen; Ivarsson, Mikael; Martin, Monique;  
Martin,  
Francois; Solary, Eric  
CORPORATE SOURCE: (1) CJF INSERM 94/08, Fac. Med., 7 Bd Jeanne d'Arc, 21033  
Dijon France  
SOURCE: Cytotechnology, (1998) Vol. 27, No. 1-3, pp. 225-235.  
ISSN: 0920-9069.  
DOCUMENT TYPE: General Review  
LANGUAGE: English  
AB Kinetic resistance plays a major role in the failure of chemotherapy towards many solid tumors. Kinetic resistance to cytotoxic drugs can be reproduced in vitro by growing the cells as multicellular spheroids (Multicellular Resistance) or as hyperconfluent cultures (Confluence-Dependent Resistance). Recent findings on the cell cycle regulation have permitted a better understanding why cancer cells which arrest in long quiescent phases are poorly sensitive to cell-cycle specific anticancer drugs. Two cyclin-dependent kinase inhibitors (CDKI) seem particularly involved in the cell cycle arrest at the G1 to S transition checkpoint: the p53-dependent p21cip1 protein which is activated by DNA damage and the p27kip1 which is a mediator of the contact inhibition signal. Cell quiescence could alter drug-induced apoptosis which is partly dependent on an active progression in the cell cycle and which is facilitated by overexpression of oncogenes such as c-Myc or cyclins. Investigations are yet necessary to determine the influence of the cell cycle on the balance between antagonizing (bcl-2, bcl-XL...) or stimulating (Bax, Bcl-XS, Fas ...) factors in chemotherapy-induced apoptosis. Quiescent cells could also be protected from toxic agents by an enhanced

expression of stress proteins, such as HSP27 which is induced by confluence. New strategies are required to circumvent kinetic resistance of solid tumors: adequate choice of anticancer agents whose activity is not altered by quiescence (radiation, cisplatin), recruitment from G1 to S/G2 phases by cell pretreatment with alkylating drugs or attenuation of CDKI activity by specific inhibitors.

L11 ANSWER 16 OF 25 MEDLINE  
ACCESSION NUMBER: 94207957 MEDLINE  
DOCUMENT NUMBER: 94207957 PubMed ID: 8156506  
TITLE: Apoptosis. Its significance in cancer and cancer therapy.  
COMMENT: Erratum in: Cancer 1994 Jun 15;73(12):3108  
AUTHOR: Kerr J F; Winterford C M; Harmon B V  
CORPORATE SOURCE: Department of Pathology, University of Queensland Medical School, Herston, Australia.  
SOURCE: CANCER, (1994 Apr 15) 73 (8) 2013-26. Ref: 179  
Journal code: 0374236. ISSN: 0008-543X.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) General Review; (REVIEW) (REVIEW, TUTORIAL)

LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
ENTRY MONTH: 199405  
ENTRY DATE: Entered STN: 19940526  
Last Updated on STN: 19950206  
Entered Medline: 19940518  
AB Apoptosis is a distinct mode of cell death that is responsible for deletion of cells in normal tissues; it also occurs in specific pathologic contexts. Morphologically, it involves rapid condensation and budding of the cell, with the formation of membrane-enclosed apoptotic bodies containing well-preserved organelles, which are phagocytosed and digested by nearby resident cells. There is no associated inflammation. A characteristic biochemical feature of the process is double-strand cleavage of nuclear DNA at the linker regions between nucleosomes leading to the production of oligonucleosomal fragments. In many, although not all of the circumstances in which apoptosis occurs, it is suppressed by inhibitors of messenger RNA and protein synthesis. Apoptosis occurs spontaneously in malignant tumors, often markedly retarding their growth, and it is increased in tumors responding to irradiation, cytotoxic chemotherapy, heating and hormone ablation. However, much of the current interest in the process stems from the discovery that it can be regulated by certain proto-oncogenes and the p53 tumor suppressor gene. Thus, c-myc expression has been shown to be involved in the initiation of apoptosis in some situations, and bcl-2 has emerged as a new type of proto-oncogene that inhibits apoptosis, rather than stimulating mitosis. In p53-negative tumor-derived cell lines transfected with wild-type p53, induction of the gene has, in rare cases, been found to cause extensive apoptosis, instead of growth arrest. Finally, the demonstration that antibodies against a cell-surface protein designated APO-1 or Fas can enhance apoptosis in some human lymphoid cell lines may have therapeutic implications.

L11 ANSWER 15 OF 25 MEDLINE  
ACCESSION NUMBER: 97174339 MEDLINE  
DOCUMENT NUMBER: 97174339 PubMed ID: 9022073  
TITLE: Drug-induced apoptosis in hepatoma cells is mediated by the CD95 (APO-1/Fas) receptor/ligand system and involves

activation of wild-type p53.

AUTHOR: Muller M; Strand S; Hug H; Heinemann E M;  
Walczak H;  
Hofmann W J; Stremmel W; Krammer P H; Galle P R  
CORPORATE SOURCE: University Hospital, Department of Internal  
Medicine IV,  
Heidelberg, Germany.

SOURCE: JOURNAL OF CLINICAL INVESTIGATION,  
(1997 Feb 1) 99 (3)  
403-13.  
Journal code: 7802877. ISSN: 0021-9738.

PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority  
Journals  
ENTRY MONTH: 199703  
ENTRY DATE: Entered STN: 19970321  
Last Updated on STN: 19970321  
Entered Medline: 19970310

AB Chemotherapeutic drugs are cytotoxic by induction of  
apoptosis in drug-sensitive cells. We investigated the mechanism of  
bleomycin-induced cytotoxicity in hepatoma cells. At  
concentrations present in the sera of patients during therapy,  
bleomycin

induced transient accumulation of nuclear wild-type (wt)  
p53 and upregulated expression of cell surface  
CD95 (APO-1/Fas) receptor in  
hepatoma cells carrying wt p53 (HepG2). Bleomycin did not  
increase CD95 in hepatoma cells with mutated p53  
(Huh7) or in hepatoma cells which were p53-/- (Hep3B). In  
addition, sensitivity towards CD95-mediated apoptosis was also  
increased in wt p53 positive HepG2 cells. Microinjection  
of wt p53 cDNA into HepG2 cells had the same effect. In  
contrast, bleomycin did not enhance susceptibility towards CD95  
-mediated apoptosis in Huh7 and in Hep3B cells. Furthermore,

bleomycin  
treatment of HepG2 cells increased CD95 ligand (CD95L)  
mRNA expression. Most notably, bleomycin-induced  
apoptosis in HepG2 cells was almost completely inhibited by  
antibodies  
which interfere with CD95 receptor/ligand interaction. These  
data suggest that apoptosis induced by bleomycin is mediated, at  
least in part, by p53-dependent stimulation of the CD95  
receptor/ligand system. The same applies to other anti-cancer drugs  
such  
as cisplatin and methotrexate. These data may have major  
consequences for  
drug treatment of cancer and the explanation of drug sensitivity and  
resistance.

L11 ANSWER 14 OF 25 MEDLINE  
ACCESSION NUMBER: 97265679 MEDLINE  
DOCUMENT NUMBER: 97265679 PubMed ID: 9111585  
TITLE: Immunochemotherapy of malignant glioma: synergistic  
activity of CD95 ligand and chemotherapeutics.

AUTHOR: Roth W; Fontana A; Trepel M; Reed J C; Dichgans J;  
Weller M  
CORPORATE SOURCE: Department of Neurology, University of  
Tubingen, School of  
Medicine, Germany.

SOURCE: CANCER IMMUNOLOGY, IMMUNOTHERAPY,  
(1997 Mar) 44 (1) 55-63.

Journal code: 8605732. ISSN: 0340-7004.  
PUB. COUNTRY: GERMANY: Germany, Federal Republic of  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199705  
ENTRY DATE: Entered STN: 19970523  
Last Updated on STN: 19970523  
Entered Medline: 19970509

AB Malignant glioma cells are susceptible to CD95(Fas  
/APO-)-mediated apoptosis triggered by agonistic antibody. Here we

examined the proapoptotic effects of the natural CD95 ligand, a  
cytotoxic cytokine homologous to tumor necrosis factor, on  
malignant  
glioma cell lines LN-229, LN-308 and T98G. We assessed whether  
glioma cell  
killing is synergistically enhanced by cotreatment with CD95  
ligand and chemotherapeutic agents, including doxorubicin,  
carmustine, vincristine, etoposide, teniposide, 5-fluorouracil and  
cytarabine. Synergy was examined at low concentrations of cytotoxic  
drugs  
and CD95 ligand with a defined effect level (IC15).  
Short-term-cytotoxicity assays showed prominent killing of the  
glioma  
cells by CD95 ligand but not by the drugs at relevant  
concentrations. CD95 ligand induced apoptosis in the  
acute toxicity paradigm was augmented by doxorubicin and  
vincristine.

Growth-inhibition assays revealed prominent synergy between CD95  
ligand and all drugs examined. The best synergy was obtained with  
CD95 ligand and doxorubicin, vincristine or teniposide. The strong  
synergistic antiproliferative effects were observed at much lower  
concentrations of CD95 ligand and cytotoxic drugs than the  
moderate synergistic acute cytotoxic effects. All cell lines examined  
express the Bcl-2 protein. LN-229 has partial wild-type  
p53 activity. T98G has mutant p53, LN-308 has a deleted  
p53 gene and lacks p53 protein expression.

Thus, synergistic effects of CD95 ligand and cytotoxic drugs  
were observed in cell lines exhibiting two features thought to play a  
role

in the chemoresistance of human malignant glioma cells: loss of  
wild-type  
p53 activity and acquisition of bcl-2 expression.  
Ectopic expression of murine bcl-2 conferred partial protection  
from CD95 ligand and drugs when administered alone but did not  
interfere with the mechanisms underlying the synergistic effects of  
CD95 ligand and chemotherapeutic drugs.

L11 ANSWER 8 OF 25 MEDLINE  
ACCESSION NUMBER: 1998416586 MEDLINE  
DOCUMENT NUMBER: 98416586 PubMed ID: 9743944  
TITLE: Molecular determinants of apoptosis induced by  
cytotoxic

drugs.

AUTHOR: Fulda S; Friesen C; Debatin K M  
CORPORATE SOURCE: University Children's Hospital, Ulm,  
Germany.  
SOURCE: KLINISCHE PADIATRIE, (1998 Jul-Aug) 210 (4)  
148-52.

Journal code: 0326144. ISSN: 0300-8630.  
PUB. COUNTRY: GERMANY: Germany, Federal Republic of  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199812  
ENTRY DATE: Entered STN: 19990115  
Last Updated on STN: 19990115  
Entered Medline: 19981216

AB Recent experimental evidence suggests that apoptosis pathways  
such as the

CD95 system are an important mediator of chemotherapy-  
induced apoptosis in various tumor cell lines. Therapeutic  
concentrations of cytotoxic drugs induce CD95 and  
CD95-L that mediates apoptosis via an autocrine/paracrine loop by  
crosslinking CD95. Interfering with CD95-L/receptor  
interaction by antagonistic antibodies to the receptor or by inhibition  
of

CD95-L expression strongly reduces apoptosis. Drug-  
induced apoptosis critically depends on activation of caspases  
since apoptosis is almost completely abrogated by the caspase  
inhibitor  
zVAD-fmk. The receptor apical caspase FLICE/MACH (caspase-8)  
and the  
downstream caspase CPP32 (caspase-3) are cleaved resulting in  
processing

of substrates such as the nuclear enzyme PARP. In addition, the response to cytotoxic drugs is modulated by pro- and antiapoptotic proteins of the

Bcl-2 family and p53. Defects in apoptosis pathways, e.g. deficient upregulation of CD95-L, downregulation of CD95 expression or blockade of caspase activation may confer resistance to cytotoxic drug treatment. Thus, chemosensitivity of tumor cells depends

on intact apoptosis pathways such as the CD95 system that are activated by chemotherapeutic drugs. These findings may have implications for drug sensitivity and resistance of tumor cells.

L11 ANSWER 6 OF 25 MEDLINE  
ACCESSION NUMBER: 1999059827 MEDLINE  
DOCUMENT NUMBER: 99059827 PubMed ID: 9841917  
TITLE: p53 activates the CD95 (APO-1/Fas) gene in response to DNA

damage by anticancer drugs.

AUTHOR: Muller M; Wilder S; Bannasch D; Israeli D;

Lehlbach K; Li-Weber M; Friedman S L; Galle P R; Stremmel W; Oren

M;

Krammer P H

CORPORATE SOURCE: Department of Internal Medicine IV, Hepatology and

Gastroenterology, University Hospital, 69115 Heidelberg, Germany.

CONTRACT NUMBER: DK373402 (NIDDK)

RO1 CA 40099 (NCI)

SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (1998 Dec 7) 188 (11) 2033-45.

Journal code: 2985109R. ISSN: 0022-1007.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

OTHER SOURCE: GENBANK-AJ011034

ENTRY MONTH: 199901

ENTRY DATE: Entered STN: 19990202

Last Updated on STN: 20000303

Entered Medline: 19990120

AB Chemotherapeutic drugs cause DNA damage and kill cancer cells mainly by apoptosis. p53 mediates apoptosis after DNA damage. To explore the pathway of p53-dependent cell death, we investigated if p53-dependent apoptosis after DNA damage is mediated by the CD95 (APO-1/Fas) receptor/ligand system. We investigated hepatoma, gastric cancer, colon cancer, and breast

cancer cell lines upon treatment with different anticancer agents known to

act via p53 accumulation. Cisplatin, mitomycin, methotrexate, mitoxantrone, doxorubicin, and bleomycin at concentrations present in the

sera of patients during therapy led to an upregulation of both CD95 receptor and CD95 ligand. Induction of the CD95 ligand occurred in p53 wild-type (wt), p53 mutant (mt), and p53 deficient (p53<sup>-/-</sup>) cell lines and at wt and mt conformation of temperature-sensitive p53 mutants. In contrast, upregulation of the CD95 receptor was observed only in cells with wt p53, not in cells with mt or without any p53. Restitution of inducible wt p53 function restored the ability of p53<sup>-/-</sup> Hep3B cells to upregulate the CD95 receptor in response to anticancer drugs. This rendered the cells sensitive to CD95-mediated apoptosis. In an attempt to understand how CD95 expression is regulated by p53, we identified a p53-responsive element within the first intron of the CD95 gene, as well as three putative elements within the promoter. The intronic

element conferred transcriptional activation by p53 and cooperated with p53-responsive elements in the promoter of the CD95 gene. wt p53 bound to and transactivated the

CD95 gene, whereas mt p53 failed to induce apoptosis via activation of the CD95 gene. These observations provide a mechanistic explanation for the ability of p53 to contribute to tumor progression and to resistance of cancer cells to chemotherapy.

L11 ANSWER 5 OF 25 MEDLINE  
ACCESSION NUMBER: 1999218643 MEDLINE  
DOCUMENT NUMBER: 99218643 PubMed ID: 10200532  
TITLE: The CD95/CD95 ligand system is not the major effector in

anticancer drug-mediated apoptosis.

AUTHOR: Tolomeo M; Dusonchet L; Meli M; Grimaudo S; D'Alessandro N;

Papoff G; Ruberti G; Rausa L

CORPORATE SOURCE: Chair of Hematology, University of Palermo, Italy.

SOURCE: CELL DEATH AND DIFFERENTIATION, (1998 Sep) 5 (9) 735-42.

Journal code: 9437445. ISSN: 1350-9047.

PUB. COUNTRY: ENGLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199905

ENTRY DATE: Entered STN: 19990614

Last Updated on STN: 19990614

Entered Medline: 19990528

AB Many anticancer drugs are able to induce apoptosis in tumor cells but the mechanisms underlying this phenomenon are poorly understood.

Some authors reported that the p53 tumor suppressor gene may be responsible for drug-induced apoptosis; however, chemotherapy-induced apoptosis can also be observed in p53 negative cells. Recently, doxorubicin (DXR) was reported to induce CD95L expression to mediate apoptosis through the CD95/CD95L system. Thus, an impairment of such a system may be involved in drug resistance. We evaluated the in vitro antitumor activity

of several cytotoxic drugs on two human p53-negative T-cell lymphoma cell lines, the HUT78-B1 CD95L-resistant cell line and the HUT78

parental CD95L-sensitive cell line. We demonstrated by Western blotting

assay that DXR and etoposide (VP-16) were able to induce CD95L expression after 4 h of treatment. In contrast, they were unable to induce the expression of p53. DXR, at concentrations ranging from 0.001 - 1 &mgr;g/ml, and VP16, at concentrations ranging from 0.05 - 1 &mgr;g/ml, were equally cytotoxic and

induced apoptosis in both cell lines as assessed by fluorescence microscopy and flow cytometry analyses. Although we observed a slightly

reduced percentage of apoptotic cells in HUT78B1 when compared with the

parental HUT78 cells after few hours of drug exposure, this difference was

no longer evident at 48 or 72 h. Similarly, the exposure of HUT78 cells to

a CD95-blocking antibody partially reduced early apoptosis (24 h) without affecting the long-term effects of the drugs including cytotoxicity. Furthermore, as observed with DXR and VP-16, both

the CD95L-sensitive and the CD95L-resistant cell lines resulted equally sensitive to the cytotoxic effects of a number of different cytotoxic drugs (vincristine, camptothecin, 5-fluorouracil and methotrexate).

The treatment with the Caspase-3 tetrapeptide aldehyde inhibitor, Ac-DEVD-CHO,

did not affect the DXR-induced apoptosis whereas it only modestly inhibited apoptosis and cytotoxicity of VP-16, while Z-VAD.FMK, a

Caspase inhibitor that prevents the processing of Caspase-3 to its active

form, was able to block DXR-induced apoptosis at 24 h but not at 48 h. Thus, our results do not confirm a crucial role for the CD95/CD95L system in drug-induced apoptosis and suggest the involvement of alternative p53-independent pathways at least in this experimental model system.

L11 ANSWER 1 OF 25 MEDLINE  
 ACCESSION NUMBER: 1999304009 MEDLINE  
 DOCUMENT NUMBER: 99304009 PubMed ID: 10200578  
 TITLE: p53-mediated up-regulation of CD95 is not involved in genotoxic drug-induced apoptosis of human breast tumor cells.  
 AUTHOR: Ruiz-Ruiz M C; Lopez-Rivas A  
 CORPORATE SOURCE: Instituto de Parasitologia y Biomedicina, CSIC, calle Ventanilla 11, 18001 Granada, Spain.  
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#### AB Induction of CD95 (Fas/APO-

1) and CD95 ligand during chemotherapeutic treatment may contribute to the death by apoptosis of some tumor cells. In

this study, we have analyzed the role of the CD95 system in genotoxic drug-induced death of human breast tumor cells. Incubation of the breast tumor cell lines MCF-7 and EVSA-T with doxorubicin or methotrexate caused apoptosis after 48 h of treatment. These drugs induced a marked increase in the level of CD95 mRNA and protein in wild-type p53-expressing MCF-7 cells. On the contrary, the breast cancer cell line EVSA-T that expresses high levels of an inactive form of p53, did not up-regulate CD95 upon drug treatment. Elevation of CD95 expression by DNA-damaging drugs was notably blocked in MCF-7 cells expressing the human papillomavirus type 16 E6 protein (E6 cells) which prevented p53 accumulation upon DNA damage. However, E6 cells were still killed

by the

drugs. Furthermore, the genotoxic drugs did not induce the expression of CD95 ligand in MCF-7 cells at doses that caused apoptosis in these breast tumor cells. Moreover, drug-induced apoptosis of breast tumor cells was not prevented in the presence of either a CD95 antagonistic antibody or a CD95 ligand blocking antibody. We also observed a strong synergism

between lower doses of DNA-damaging drugs and CD95 agonistic antibody in the induction of apoptosis in MCF-7 cells. In summary, our data indicate that drug-induced apoptosis of breast tumor cells occurs by a CD95/CD95L-independent mechanism although by elevating the tumor suppressor proteins p53 and CD95, genotoxic drugs may sensitize breast tumor cells to CD95-mediated apoptosis.

=> d his

(FILE 'HOME' ENTERED AT 09:53:39 ON 02 SEP 2002)

FILE 'MEDLINE, BIOSIS, CAPLUS, CANCERLIT' ENTERED AT 09:54:18 ON 02 SEP 2002

L1 37622 S CD95 OR FAS OR APO-1  
 L2 10247137 S INCREASES OR INDUC?  
 L3 22697 S L1(S)L2  
 L4 2705546 S EXPRESS?  
 L5 13033 S L3(S)L4  
 L6 104368 S P53

L7 953 S L5(S)L6  
 L8 439321 S CHEMOTHERAP?  
 L9 112 S L7 AND L8  
 L10 46 DUP REM L9 (66 DUPLICATES REMOVED)  
 L11 25 S L10 NOT PY>1999

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